REMARKS

The Office Action dated September 12, 2007, has been reviewed, and the comments of the U.S. Patent Office have been considered. Claims 20 -22 and 24 – 28 stand rejected. As discussed in detail below, Applicant respectfully submits the Patent Office has failed to support the burden imposed when advancing such rejections. Claims 1-19 and 27-50 are withdrawn from consideration, but remain pending. The Examiner is authorized to cancel these claims in favor of the filing of a divisional application upon indication of the allowability of the few claims Examined herein.

REJECTIONS OF CLAIMS 20-26 UNDER 35 U.S.C. § 112, FIRST PARAGRAPH

Claims 20-22 and 24-26 stand rejected under 35 U.S.C. § 112, first paragraph, for allegedly failing to comply with the enablement requirement. This rejection is respectfully traversed

A. The Action Does Not Consider the Wands Factors, Which Support Enablement

In advancing a rejection for lack of enablement, it is the burden of the Office to demonstrate why the evidence advanced in the Application as originally filed is inadequate to demonstrate that one of skill in the art, could, after the exercise of exhaustive but non-inventive work, arrive at the subject matter claimed. In this case, the subject matter claimed is the ***treatment*** of a viral infection by administration of an antibody to TSG101 (the claims go on to specify the antibody in terms of its binding epitope). The Examiner does not question that the antibodies can be made – indeed, the specification is replete with examples of such antibodies. The Examiner does not question that those antibodies, when administered to virally infected cells

and cell systems, do in fact "treat" the infection by blocking or reducing viral replication. The examiner does not question that the antibodies described could not be administered to humans or other mammals. There is abundant discussion of the same in the specification.

Rather, the ONLY basis for rejecting all claims as lacking enablement is the Examiner's assertion, unsupported by reference to any authority or publication whatsoever that:

> Those of skill in the art recognize that artificial or surrogate *in vitro* assays are generally useful to observe basic cellular phenomenon, such as virus "budding". However, the correlation of the physiological condition *in vivo* is generally lacking because cells used such artificial or surrogate *in vitro* assays cannot support the full replication cycle of viruses, such as HIV infection in 293 cells. The specification has not provided any evidence that anti-TSG101 antibodies effectively inhibit virus infection by competing with the rate of virus replication. Office Action, p. 2 -3.

Respectfully, the Examiner is wrong in at least three pertinent respects. Moreover, Applicant submits herewith evidence including acellular, cellular, and *in vivo* evidence demonstrating the effectiveness of the claims method against viral infection. It is noted in this respect that the virus against which *in vivo* effectiveness is one of the most widely recognized virulent viruses of the world, Ebola.

However, it is the burden of the Office, not applicant, to advance evidence in support of the rejection. The factors to be considered in determining enablement, particularly in a biotechnology setting, are well established. They include the level of skill in the art, which is extraordinarily high. They include the background of the art. Surely, by now it is well established that antibodies, such as the type recited, shown to be effective in inhibiting agents *in vitro* go on, through well established testing protocols, to show the same effect in vivo. Many of these, such as Herceptin (breast cancer) are directed not against the invader, but, like the claimed invention, a host protein (HER3). The factors to be considered include the amount of guidance and

examples, which are abundant in the specification. And the law makes it clear that the Applicant's scientific rationale, explained in the pending application, if supported by data, as it is here, must be accepted in the absence of countervailing evidence. The Examiner has advanced no such evidence. The law is clear *In re Wands*, 8 USPQ2d 1400 (Fed Cir 1988) requires the Examiner to consider the factors enunciated, and demonstrate those which support a conclusion that the case is not enabled. This the Examiner has not done.

The *Wands* factors support Applicant's claims. The claims are not broad – the active agent is confined to two small epitopes. The nature of the invention replicates proven methods – antibodies directed against host proteins shown to be implicated in the chain of events leading to the disease. The prior art teaches us in great detail about how to prepare and administer antibodies for this purpose – just not THESE antibodies. The level of skill is high. This art is neither highly unpredictable nor highly predictable. It calls for experimentation of the type reflected by the specification. Once that evidence has been advanced, the prospect of success becomes more likely. The specification provides abundant direction in terms of antibody preparation, administration, and evidence of effectiveness. The application is replete with working examples. The quantity of the experimentation needed to take the invention forward on the basis of the disclosure – administering the antibodies to animals, is neither complex nor undue. **Of the eight factors to be considered, at least 7 support a conclusion of enablement.** Under these circumstances, more than some "doubt" must be expressed by the Examiner. Concrete explanation of which factors are not so supported is required. The Office Action is devoid of such discussion, because no factor weighs against enablement. In the absence of a

discussion of the type of consideration sanctioned by the Courts to address enablement, the rejection must be withdrawn.

B. The Examiner's Rejection is Based On Unsupported Speculation

The core of the Examiner's position is that the evidence advanced in the specification is unpersuasive because those of skill in the art would not accept it as predictive of effectiveness *in vivo*. Respectfully, such an assertion must be backed by evidence. The literature is abundant in relying on this type of evidence to identify antibodies likely to be effective in treating mammalian conditions. In this respect, the fact that the necessary experimentation is complex does not make it undue if *it is commonly undertaken in the industry. M.I.T. v. Fortia*, 227 USPQ 428 (Fed. Cir. 1985). Applicant has proceeded in exactly the fashion followed by 1000s of researchers in medicine. Where the Examiner's rejection is based on a lack of alleged correlation between *in vitro* and *in vivo* results, the Examiner must come forward with concrete evidence that the model is not a good one, that the evidence does not correlate. And even then, he must weigh the evidence. *In re Brana*, 34 USPQ2d 1436 (Fed. Cir. 1995).

Here, the Examiner points to no evidence of any sort that suggests there is a lack of correlation. There is no reason to assume that the inhibition of virion formation demonstrated in the experiments and examples reported will not be repeated in the mammalian body. Rather, the Examiner asserts that because certain 293 kidney cells cannot support a full HIV infection cycle, the information is in doubt. Respectfully, you do not have to support such a cycle to show inhibition, nor are Applicant's examples limited to 293 cells. Moreover, with respect, the Examiner is either incorrect or the reliance on a phenomenon associated with 293 cells is not clear. 293 cells are well characterized in the art, and Applicant points to, as an example only,

U.S. Patent 6,015,694 which uses 293 cells to generate virus particles through infection of the same with viruses that carry a foreign or trans gene. Applicant's invention is not limited to HIV. The burden imposed on the Examiner – when the basis for lack of enablement is not any of the *Wands* factors but simply correlation alone, has not been met. Respectfully, the rejection should be withdrawn.

C. Evidence of *In Vivo* Effectiveness Is Submitted Herewith

To put to rest the question of correlation, Applicant submits herewith the entirety of U.S. Patent Application 11/940,714, commonly assigned herewith. The propriety of reliance on data in another application for enablement is well established. *Ex parte Ebata.* This application demonstrates, *with the exact antibodies recited in the claims herein*, inhibition of viral activity in acellular matrices, in cells and cell systems, **and *in vivo*, in widely accepted mammalian models for viral treatment – mice.** While the Examiner is invited to consider the entirety of the application for the further evidence of the efficacious nature of the antibodies recited, the Examiner's attention is respectfully directed to Figure 27, and the specification at pages 81-82, which clearly shows that the antibodies recited in the examined claims were effective in protecting mice against Ebola virus infection. The data that the law says is unnecessary, but the Examiner insists upon, is now of record. Accordingly, withdrawal of the rejection of all claims for lack of enablement is respectfully requested.

REJECTIONS OF CLAIMS 20-22, 24 AND 25 UNDER 35 U.S.C. § 103(A)

Claims 20-22, 24 and 25 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over U.S. Patent Application Publication No. 2004/0109861 (**Zavitz**). This rejection is respectfully traversed.

Certain, but not all, of the Claims examined stand rejected as obvious. To render a claim obvious, all the recited elements must be part of the prior art, and characterized such that one of skill in the art would have found their combination, in the manner recited in the claims, desirable or necessary. Not only does the art cited by the Examiner not do this, it is not even prior art at all.

A. Zavitz Is Not Available as Prior Art

In Applicant's response of June, 2007, it was noted that the disclosure of **Zavitz** relied upon by the Examiner (paragraphs 241 and 242) was not present in the application filed May 14, 2002 (PCT/US02/08146) from which **Zavitz** claims priority, or the provisional application from which that CIP parent claims priority. As such, **Zavitz** is not prior art against the claims. Applicant went through this discussion specifically so the Examiner could cite to that portion of the priority document on which he relies. It is noted that, *imprimus*, it is the burden of the Examiner to demonstrate that date, not for Applicant to disprove it. MPEP 706.

As Applicant anticipates the filing of an appeal brief, the citation by the Examiner of the portion(s) of the provisional application he relies on would have been of value in focusing the issue. Rather, in the outstanding office action, the Examiner asserts, without citation or support, that the "provisional application 60/276,259 …has full support for antibody therapy using anti-TSG101 (antibodies)." (parenthetical supplied). Respectfully, this bland assertion, where the

specific disclosure in **Zavitz** relied upon by the Examiner for the rejection is missing from the provisional, is inadequate.

As noted, the Examiner relies on antibody therapy paragraphs 241 and 242. A comparison with the provisional application shows this disclosure to be quite different. The description of antibodies suitable for use in the provisional does not include anti-TSG101 antibodies. Instead, it refers to antibodies that are "selectively immunoreactive with a protein complex" which includes TSG101 bound to something else! Importantly, the provisional application teaches "the antibody is not substantially immunoreactive with the interaction protein members of the protein complex." USSN 60/276,259, p. 37. What the provisional application is teaching is to NOT use an antibody that binds to TSG101, and certainly not one that is confined to epitopes found on TSG101 only, but rather, something that binds the complex of two or more proteins.

The portion of the provisional application that is directed to antibodies is at pages 37 – 42. Pages 37 – 41 are devoted to antibodies that bind to the protein complex, but not the members of that complex. Pages 41 – 42 are directed to bifunctional antibodies that bind to two members of the complex. Applicant's antibodies are not only not taught, they are taught away from.

Moreover – as the Examiner recognizes, the teaching in this provisional application must be enabling, at least as to one species, to support the rejection. There is NO antibody identified anywhere in the provisional application, prophetic or actual. There is no method of administration described. There are no dosage values and no protocols. How then is this

document "enabling." **Zavitz** is NOT prior art, and the rejection should be withdrawn on that ground.

B. Zavitz Does Not Teach the Elements of the Rejected Claims

Each of the claims rejected for obviousness recites, as a key provision;

wherein said antibody binds an epitope in a region selected from the group consisting of VRETVNVITLYKDLKPVL (SEQ ID NO:2) and QLRALMQKARKTAGLSDLY (SEQ ID NO:3)

Although many of the claims are narrower than this simple limitation, all of them require the use of these very specific antibodies. The Examiner acknowledges that this is not taught, but asserts it would have been obvious to select these epitopes given **Zavitz**. Why? Because, the Examiner reasons, the art was aware that TSG101 has an N terminal region that includes a ubiquitination domain of residues 2 – 145 which "is responsible for interaction between TSG101 and viruses." Office Action, p. 5. This is simply wrong.

It may have been clear that residues 2 – 145 of TSG101 feature a UVE domain, although the Examiner cites to no support for this proposition other than Applicant's own specification. **What was clearly not known at Applicant's filing date is this is the domain where TSG101 interacts with viruses.** Indeed, Applicant respectfully submits this must be wrong, because its C-terminal antibodies work quite well! If the Examiner is to maintain this rejection, specific citation to that portion of the reference relied on is certainly requested.

Beyond this however, Applicant submits that the reference teaches nothing at all about what epitopes to select for binding. Simply because TSG101 has a UVE domain does not make it a candidate for treatment of viral infections. TSG101 is a host protein – why would you direct an

antibody against the UVE domain of a host protein to defeat a viral invader, absent Applicant's disclosure? The reference doesn't tell you to do this.

But wait – there's more. Even if you somehow grant the Examiner's position that you would pick this N-Terminal UVE domain for reasons not explained – that region, according to the Examiner himself, is 143 residues long! Why on earth would you pick the 18 residues selected? More importantly – why "on **Zavitz**?" The sole reference advanced certainly does not teach this element, or indeed, anything at all about what epitope to select.

Knowing what the structure of TSG101 is, or its various domains, tells you absolutely nothing about what domains to bind to in order to block viral replication. **Zavitz** teaches you nothing about this. Indeed, the only region **Zavitz** mentions as a good place to bind is the luecine zipper toward the middle of the molecule. It is not enough to show that the sequence of TSG101, which obviously includes the epitopes selected, was known. Rather, it must be shown that those of skill in the art appreciated that they would serve as good binding sites for the purposes of inhibiting viral infection. **Zavitz** does not mention ANY site as so useful, much less the two recited in the claims. The rejection advanced does not meet minimum standards for teaching the elements of the claims. It should be withdrawn. The same is respectfully requested.

CONCLUSION

In view of the foregoing evidence and remarks, Applicant respectfully requests reconsideration of this Application and the prompt allowance of at least Claims 20-22 and 24-26.

Should the Examiner feel that there are any issues outstanding after consideration of this response, the Examiner is invited to contact the undersigned to expedite prosecution of the application.

Respectfully submitted,

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